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Using Cost-Effectiveness Thresholds to Determine Value for Money in Low- and Middle-Income Country Healthcare Systems: Are Current International Norms Fit for Purpose?

CHE Research Paper 98

Using cost-effectiveness thresholds to determine value for money in low- and middle-income country healthcare systems: Are current international norms fit for purpose?

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Abstract

Healthcare systems in low- and middle-income countries face considerable population healthcare needs with markedly fewer resources than those in higher income countries. The way in which available resources are allocated across competing priorities has a profound effect on how much health is generated overall, who receives healthcare interventions and who goes without. Judgements about whether interventions and programmes should be regarded as cost-effective and prioritised over others should be based on an assessment of the health benefits that will be lost because the resources required will not be available to implement other effective interventions and programmes that would benefit other patients in the same or different disease areas. Unfortunately, frequently adopted international norms, in particular the cost-effectiveness thresholds recommended by the World Health Organization (WHO), are not founded on this type of assessment. Consequently current judgements about which interventions and programmes are cost-effective are often aspirational and do not reflect the reality of resource constraints. As a consequence their use is likely to reduce overall population health and exacerbate healthcare inequalities. They also fail to identify the real (and greater) value of devoting more resources to these efforts. By obscuring the true implications of current arrangements they do not contribute to greater understanding of and accountability for global and local decisions made on behalf of others in low and middle as well as in high income countries. We illustrate these points using examples from HIV/AIDS.

Introduction

It is estimated that in 2010, US$6.5 trillion was spent on health across the globe.[1] Somewhat incongruously expenditure on health is least where need is greatest – only fifteen percent of this total is spent in low- and middle-income countries, where eighty five percent of people live and who suffer from ninety-two percent of the world's disease burden.[1] Global health expenditure is estimated at $948 per person per year on average but varies enormously; from just US$12 in Eritrea to US$8362 in the United States.[1] Many countries lack access to basic, often lifesaving, interventions and healthcare infrastructures are fragile - in Kenya, for instance, 43% of health facilities lack a minimally defined infrastructure; and in Uganda 63% of lower-level facilities don't have drugs to treat even basic conditions.[2] This suggests that the health gains from any additional funding are likely to be high (i.e. high marginal productivity of health care).

To address this imbalance between healthcare spending and need, efforts are made internationally to increase healthcare expenditures and to improve health attainment in the world's lower income regions. In 2012, it is estimated US$28.1 billion was spent on development assistance for health (DAH) from higher to lower income countries - a large proportion going to sub-Saharan Africa and committed to specific disease areas such as HIV/AIDS, tuberculosis, and maternal, new-born and child health.[3] Funding comes from a range of bilateral (i.e. country-to-country) and multilateral donors (e.g. World Bank, Global Fund), as well as non-governmental organizations/charities and philanthropic organizations. Such efforts, in addition to significant domestically-sourced funding, make the financing architecture for healthcare in lower incomes very complex.

A major focus for international efforts is HIV/AIDS. It was estimated that in 2009 external financing accounted for 80-100 percent of total national HIV/AIDS programme spending in 12 out of 21 sub-Saharan African countries,[4] the region under the greatest burden from the disease, although domestic contributions to programmes are generally growing.[3] In addition to funding, countries also look externally for guidance on the design of their HIV/AIDS programmes, in particular from the World Health Organisation ((WHO) which has produced and regularly updated guidelines on management of HIV since 2003; the latest update being new 2013 Consolidated Guidelines for Antiretroviral Therapy (ART)[5] for use in low and middle income countries. WHO also issues guidelines for the treatment and management of a number of other diseases; such as for child health[6], malaria[7], chronic non-communicable diseases[8] as well as others.

This picture of multi-layered financing and policy influence raises difficult questions about how HIV treatment as well as other healthcare interventions should be prioritized within low- and middle-income countries. It also poses questions regarding how much funding should be committed to specific disease areas, for instance to HIV as opposed to say malaria, as well as which alternative interventions within these disease areas ought to be implemented, and for which specific populations. For example, 'Should resources be committed - by both domestic and international authorities - to HIV prevention, cotrimoxazole prophylaxis, or to HIV treatment?'; 'Who should be eligible for interventions – everybody or specific populations?'; and 'Should priority be given to HIV treatment and/or prevention or instead should resources be committed to meet other healthcare priorities altogether, such as to malaria treatment or the management of non-communicable diseases?'

This paper examines these issues using examples from HIV/AIDS; although the same issues also arise when considering choices faced in other diseases. It outlines how domestic governments and their development partners could decide to allocate resources both within and between healthcare programmes to generate health gains for their populations.

Allocating resources within HIV treatment programmes

Given reliance on external funding and the role of international guidelines, the setting of country-specific HIV treatment policies depends upon both domestic and international influences.

The 2013 WHO ART Guidelines outline global norms and standards intended to be "progressively realized" by countries. Key recommendations are outlined in Table 1. The guidelines are aspirational; recommending the use of new and more expensive treatments and it appears that one intention is to close perceived gaps in ART standards between high and lower incomes settings. However, large gaps in ART coverage still remain in many areas of the world. In sub-Saharan Africa, only an estimated 68% of adults and 32% of children with HIV have access to ART if given according to the more modest 2010 guidelines; and coverage is much lower if ART is prescribed according to WHO 2013 guidelines where earlier initiation of ART is recommended.[9] An important question is whether countries should commit to more ambitious approaches to ART (e.g. newer, more expensive ART with earlier initiation) or, firstly, to close gaps in treatment coverage for the most sick with current interventions.

Table 1: Key new recommendations in 2013 WHO consolidated HIV treatment guidelines

Topic	2010 WHO guideline recommendations	2013 WHO guideline recommendations	Quality of evidence supporting recommendations
When to start antiretroviral therapy	CD4 ≤ 350 - Irrespective CD4 for TB & HBV	CD4 ≤ 500	Moderate
Patient monitoring when on ART	Clinical or CD4 Monitoring Phase in of viral load testing	Viral load monitoring	Low
PMTCT interventions	Option A (AZT +infant NVP) Option B (triple ARVs)	Lifelong ART for all pregnant or breastfeeding women irrespective of CD4 count (Option B Plus)	Low
When to start ART in children	ART initiated in all children under two years of age - Irrespective CD4	ART initiated in all children under five years of age - Irrespective CD4	Very low
Paediatric 1st line ARVs (in children <3 years only)	NNRTI based regimen	PI based regimen - regardless of NNRTI exposure	Moderate

A notable recommendation of the 2013 WHO ART Guidelines is the use of routine viral load monitoring (VLM) of patients on ART, instead of currently used CD4 testing and/or clinical monitoring approaches. VLM is routinely used in well-resourced settings to provide information on patient adherence and to guide rapid switching of ART to prevent development of resistance. However, in these settings patient management is individualised with good availability of many antiretroviral drugs for second and third-line treatment and beyond. In most lower income settings, only two lines of ART treatment are available, and rapid switching to much more costly secondline ART may not be the best approach. Furthermore, although some observational evidence indicates VLM is effective at improving adherence,[10] improved clinical effectiveness has not been substantiated in randomized control trials.[11,12] It has also been suggested that VLM may reduce

unnecessary switching to second-line ART (when VL is undetectable)[13] and could, through reduced viral load, lower onward transmission of HIV.[14] However, VLM is also the most expensive of the possible monitoring approaches, with a viral load test costing $45 compared to $9 for a CD4 test and only the cost of a clinic visit for clinical monitoring.[12]

To determine whether particular HIV treatment approaches, such as use of VLM, represent value for money within particular settings requires assessing whether expected health gains are worth the cost. It is important to assess the criteria on which value-for-money (i.e. cost-effectiveness) is judged. Some previous studies have indicated that VLM, despite its uncertain clinical benefit, is expected to be cost-effective even in sub-Saharan African settings (see Walensky et al.[15] for review of studies as of 2010). The studies finding routine VLM to be cost-effective were assessed against WHO recommendations that deem an intervention offering a unit of health gain (disability adjusted life year (DALY) averted, a measure of survival and morbidity) at under 3 times GDP per capita in a country to be "relatively cost-effective" and one less than 1 times GDP per capita "highly cost-effective".[16] However, although widely adopted, there appears to be no empirical or theoretical basis behind these benchmarks.[17]

A more recent study, undertaken by the HIV Modelling Consortium to inform the 2013 WHO Guidelines, followed a different approach to cost-effectiveness analysis by assessing how HIV programme resources could be alternatively used. [12] Previous studies had indicated that ART with lower cost clinical monitoring delivers health gains at around US$600 per DALY-averted compared to no ART. [18-20] Therefore, as a result of incomplete current coverage, resources could alternatively be spent on ART with clinical monitoring at a cost of $600 per DALY. The study estimated costs per DALY-averted associated with routine VML provision of $3,500-$6,000.[12] Although within the range of 3 times GDP per capita for many countries this was well above the indicative $600 benchmark so VLM was judged very unlikely to be cost-effective in most circumstances (i.e. as additional funding would generate more health if used to expand current incomplete coverage rather than increase use of VLM).

The choice of criteria to assess value for money/cost-effectiveness therefore determines which interventions are recommended for delivery. Previous studies that used one approach to assess value for money come to the opposite conclusion to another using a different approach. This was not as a result of marked differences in estimated costs and health outcomes, but solely on the basis of how value for money was assessed. So the question is, 'Which approach should policy-makers use?'

Table 2 sets out a stylized example of a situation in which a country is limited in its overall resources and needs to decide how to spend these across ART alternatives. Parameters are chosen to reflect a situation similar to that in Cameroon, a country with an estimated ART eligible population (at CD4<350) of 590,000[21] and purchasing power parity (PPP) GDP per capita of US$2,312[22] in 2013. We assume current ART coverage of 51%.[9] Illustrative per patient costs and health attainment (measured in quality-adjusted life years (QALYs) a generic measure of health) are shown. These result in a cost-per-QALY gained of $1,000 for ART with clinical/CD4 monitoring compared to no ART and $3,000 for ART with VLM compared to ART with clinical/CD4 monitoring.

Table 2: Stylized current state of ART provision in Cameroon with clinical/CD4 monitoring

	Illustrative per patient total costs	Illustrative per patient total health attainment (QALYs)	Incremental cost-effectiveness ratio (ICER)	ART coverage	Health attainment (QALYs)	Illustrative total costs
No treatment	$2000	5	-	49%	1.45m	$602m
ART with clinical/CD4 monitoring	$22000	25	$1000 per QALY	51%	7.52m	$6,620m
ART with VL monitoring	$28000	27	$3000 per QALY	*0%*	*0*	*$0*
				Total	**8.97m**	**$7,722m**

Note: Approx. ART eligible (CD4<350) adult population of Cameroon, 2012, is 590,000.[9]

We assume that additional resources are committed to the ART programme (either by Government or donor partners) which increase the available budget by 25% over the evaluated period. This can either be used to provide (i) VLM to all those currently receiving ART with clinical/CD4 monitoring (Table 3a); or (ii) ART based upon clinical/CD4 monitoring for those not currently receiving ART (Table 3b). The former VLM approach is estimated to lead to overall population health gain of 0.6million QALYs; this would be deemed cost-effective according to the WHO recommended benchmark of 3 times GDP per capita. However, expanding HIV testing and ART availability to those in need would increase population health by 1.8million QALYs (3 times the amount; the ratio of ICERs). Moreover, it would lead to more equal population health outcomes with a 16% increase in ART coverage.

This example is characteristic of many real policy decisions. Applied cost-effectiveness analyses in HIV/AIDS[23,24] and other disease areas[25,26] routinely make recommendations on the basis of WHO cost-effectiveness thresholds, aiming to promote access to new and more expensive therapies. However, whenever there are gaps in coverage of current interventions, as is typically the case in low- and middle-income countries, due to finite resources, the promotion of new and more expensive therapies risks lowering overall population health attainment and increasing health inequalities. Economic theory would highlight that the only justifiable way to inform priorities is to adopt an approach that carefully considers how else resources can be used to improve health.[27]

Table 3: Alternative ways of spending ART programme resources

(a) Invest in viral load monitoring

	Illustrative per patient total costs	Illustrative per patient total health attainment (QALYs)	Incremental cost-effectiveness ratio (ICER)	ART coverage	Health attainment (QALYs)	Illustrative total costs
No treatment	$2,000	5	-	49%	1.45m	$602m
ART with clinical/CD4 monitoring	$22,000	25	$1000 per QALY	0%	-	-
ART with VL monitoring	$28,000	27	$3000 per QALY	51%	8.12m	$8,425m
				Total	**9.57m**	**$9,027m**

(b) Invest in ART scale-up

	Illustrative per patient total costs	Illustrative per patient total health attainment (QALYs)	Incremental cost-effectiveness ratio (ICER)	ART coverage	Health attainment (QALYs)	Illustrative total costs
No treatment	$2,000	5	-	34%	0.99m	$395m
ART with clinical/CD4 monitoring	$22,000	25	$1000 per QALY	67%	9.81m	$8,632m
ART with VL monitoring	$28,000	27	$3000 per QALY	0%	-	-
				Total	**10.80**	**$9,027m**

Note: Approx. ART eligible (CD4<350) adult population of Cameroon, 2012, is 590,000.[9]

Allocating resources between HIV Treatment and other healthcare programmes

Many working in specific disease areas will consider the comparison just presented unfair. They may ask, 'Why can't resources be committed to both VLM and ART scale-up?' The 2013 WHO ART Guidelines are aspirational and were perhaps developed in the hope that once policies are set, resources will follow. The problem is that this 'aspirational approach' does not address the question of how best to use existing resources to have the greatest impact on health outcomes. In fact, failing to properly take account of existing constraints on resources can lead to decision that make matters worse if resources are reallocated from more effective programmes and interventions, possibly in other disease areas, in an attempt to achieve these aspirations. It also obscures the implications of the reality of existing constraints and does not highlight the potential health effects of increasing the resources available. Moreover, HIV/AIDS is not the only disease area with worthy claims on such healthcare resources, although some budget allocations may have to be spent on HIV as a result of funder specifications. It is appropriate then to question whether resources spent on HIV treatment policies (e.g. by following the WHO Guidelines) would generate more or less health

than spending on other healthcare needs. The WHO cost-effectiveness benchmarks in no way reflect this assessment.

As highlighted previously, interventions in many disease areas are not fully provided and could generate health gains at comparatively low cost. Childhood interventions, particularly vaccinations, often provide greatest value yet remain underprovided - rotavirus vaccination, for instance, has been associated with a cost-per-DALY-averted of $43;[28] and treatment of severe malnutrition costs $53 per DALY-averted.[29] Even within HIV, prevention of mother-to-child HIV transmission costs below $150 per DALY-averted using available intervention;[30] yet a coverage gap of 38% remains across low- and middle-income countries.[9] The lack of basic health care implies that if extra resources are available there are areas where very large health gains could be achieved for minimal spending.

Is there a way out of the straightjacket of resource constraints?

The approach of 'aspiration first' tends to rally civil society, patient advocacy groups and healthcare practitioners – providing interventions that are deemed amongst the best available seems a worthy cause. However, when resources are committed to areas other than where they will generate greatest gains this results in real losses in health for individuals and society as a whole.

The use of WHO recommended cost-effectiveness benchmarks of 1 and 3 times GDP per capita has no theoretical or empirical basis. Analyses using these benchmarks have the tendency to make almost all healthcare interventions notionally 'cost-effective' even in the most resource constrained countries. Perhaps they were designed for this intent? However, they stand in stark contrast to disturbing levels of unmet need within low- and middle-income countries and, in all likelihood, exacerbate this situation. They take no account of whether resources could be better used elsewhere.

As means of comparison, the most comprehensive assessment of health forgone through resources being committed to particular interventions is from the UK.[31] This estimates a benchmark of 0.52 GDP per capita in that country. Lower income countries commit a lower proportion of their GDP to prepaid pooled healthcare funding than higher income countries like the UK[32] and it has been suggested the relationship between healthcare spending and health attainment across countries is subject to diminishing returns.[1,33] Thus a reasonable conclusion would be that a suitable benchmark for lower income countries is unlikely to be higher than 0.52 GDP p.c. and may well be considerably lower.

It may be claimed that any resources committed to particular interventions from outside of a country are additional to those otherwise available and so do not impose opportunity costs on the country's limited budgets. However, external funds could also be used for other purposes – even if in other jurisdictions. It should be hoped that external funders commit resources to where they will generate greatest gains; given high need and constrained financing, this will generally be in the lowest income settings. The way in which external resource commitments are made requires scrutiny in this respect.

It may also be queried whether the overall level of resources committed to healthcare is appropriate in a country. This requires assessing whether more or fewer resources should be devoted to health relative to other economic activities and societal concerns. Although this is ultimately a political question, it can be informed by examining local public preferences for forgoing non-health forms of consumption to achieve improved population health. It is certainly not the role of the WHO to state how much should be spent on healthcare within jurisdictions. Furthermore, it is highly unlikely this should be at a level of 1-3 times GDP per capita, which implies spending more per person-year on

health than the total per person economic output. Even if health should be funded to this level, there would be no justification for not spending first on interventions offering greatest health gains.

There appears no way out of the straightjacket of resource constraints; yet this is no reason for despair.   Recognizing constraints and acting within them is the route to providing greatest health benefits to the population from the means available.   It is only by being explicit about the reality of the implications of the resources currently available that the value of devoting more resources to these efforts can properly be highlighted. In this sense, economic analysis founded on an evidence based approach to judging cost-effectiveness in low and middle income countries can also contribute to holding global and local decision makers, as well as wider society, to account (and enable informed reflection) on the adequacy and the justice of current arrangements.

Key Messages

- Efficient allocation of limited resources requires using these resources where they can generate greatest benefits.
- This requires policymakers to carefully assess which interventions provide greatest health gains from limited resources available and not to fund interventions which for go more health benefits than they generate.
- Widely employed resource allocation norms recommended by the World Health Organization (WHO; i.e. cost-effectiveness thresholds based upon gross domestic product (GDP) per capita) conflict with the central principles of resource allocation. Their continued use risks reducing population health and exacerbating health inequalities in some of the poorest countries in the world.
- Judging cost-effectiveness instead based upon the reality of resource constraints would facilitate understanding of the value of committing more resources to healthcare. It would also contribute to holding global and local decision-makers, and society more generally, to account by enabling informed reflection on the adequacy and justice of current arrangements.

Bibliography

1.   World Health Organization. *Spending on health: a global overview*. 2012; http://who.int/mediacentre/factsheets/fs319/en/index.html. Accessed 17/2/2014, 2014.

2.   World Bank. *Service delivery indicators.* http://data.worldbank.org/topic/health. Accessed 18/2/2014, 2014.

3.   Institute for Health Metrics and Evaluation. *Financing global health 2012: the end of the golden age?* 2013.

4.   Haacker M. Financing HIV/AIDS programs in sub-Saharan Africa. *Health Affairs.* Nov-Dec 2009;28(6):1606-1616.

5.   WHO. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach.* 2013.

6.   World Health Organization. Pocket book of hospital care for children*.* 2013.

7.   World Health Organization. *Guidelines for the treatment of malaria* (2nd edition). 2010.

8.   World Health Organization. *Prevention and control of noncommunicable diseases: guidelines for primary health care in low resource settings*. 2012.

9.   UNAIDS. *Global report: UNAIDS report on the global AIDS epidemic 2013.* 2013.

10.   Bonner K, Mezochow A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *Journal of Acquired Immune Deficiency Syndromes.* Sep 1 2013;64(1):74-78.

11.   Jourdain G, Le Coeur S, Ngo-Giang-Huong N, et al. Switching HIV treatment in adults based on CD4 count versus viral load monitoring: a randomized, non-inferiority trial in Thailand. *PLoS Med.* Aug 2013;10(8):e1001494.

12.   Keebler D, Revill, P., Braithwaite, S. Cost-effectiveness of different strategies to monitor adults on antiretroviral treatment: a combined analysis of three mathematical models. *Lancet Global Health.* 2014;2(1).

13.   Sigaloff KC, Hamers RL, Wallis CL, et al. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. *Journal of Acquired Immune Deficiency Syndromes.* Sep 1 2011;58(1):23-31.

14.   Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS.* Jul 17 2009;23(11):1397-1404.

15.   Walensky RP, Ciaranello AL, Park JE, Freedberg KA. Cost-effectiveness of laboratory monitoring in sub-Saharan Africa: a review of the current literature. *Clinical Infectious Diseases :An Official Publication of the Infectious Diseases Society of America.* Jul 1 2010;51(1):85-92.

16. WHO. World Health Organization, Cost-effectiveness thresholds. http://www.who.int/choice/costs/CER_thresholds/en/index.html. 2012. Accessed April 30, 2012.

17. Revill P, Sculpher M. Cost effectiveness of interventions to tackle non-communicable diseases. *BMJ.* 2012;344:d7883.

18. Braithwaite RS, Nucifora KA, Yiannoutsos CT, et al. Alternative antiretroviral monitoring strategies for HIV-infected patients in east Africa: opportunities to save more lives? *Journal of the International AIDS Society.* 2011;14:38.

19. Goldie SJ, Yazdanpanah Y, Losina E, et al. Cost-effectiveness of HIV treatment in resource-poor settings--the case of Cote d'Ivoire. *The New England Journal of Medicine.* Sep 14 2006;355(11):1141-1153.

20. Bishai D, Colchero A, Durack DT. The cost effectiveness of antiretroviral treatment strategies in resource-limited settings. *AIDS.* Jun 19 2007;21(10):1333-1340.

21. Diabetes Care. Eye care guidelines for patients with diabetes mellitus. Vol 131990:14-15. REF NEEDS COMPLETING

22. World Bank. *World Bank open data*. http://data.worldbank.org/. Accessed 24/2/2014, 2014.

23. Levison JH, Wood R, Scott CA, et al. The clinical and economic impact of genotype testing at first-line antiretroviral therapy failure for HIV-infected patients in South Africa. *Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America.* Feb 2013;56(4):587-597.

24. Walensky RP, Cohen MS, Freedberg KA. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. *The New England Journal of Medicine.* Feb 6 2014;370(6):581-582.

25. Ortegon M, Lim S, Chisholm D, Mendis S. Cost effectiveness of strategies to combat cardiovascular disease, diabetes, and tobacco use in sub-Saharan Africa and South East Asia: mathematical modelling study. *BMJ.* 2012;344:e607.

26. Chisholm D, Baltussen R, Evans DB, et al. What are the priorities for prevention and control of non-communicable diseases and injuries in sub-Saharan Africa and South East Asia? *BMJ.* 2012;344:e586.

27. Palmer S, Raftery J. Economic notes: opportunity cost. *BMJ.* Jun 5 1999;318(7197):1551-1552.

28. Atherly D, Dreibelbis R, Parashar UD, Levin C, Wecker J, Rheingans RD. Rotavirus vaccination: cost-effectiveness and impact on child mortality in developing countries. *The Journal of Infectious Diseases.* Nov 1 2009;200 Suppl 1:S28-38.

29. Bachmann MO. Cost-effectiveness of community-based treatment of severe acute malnutrition in children. *Expert Review of Pharmacoeconomics & Outcomes Research.* Oct 2010;10(5):605-612.

30. Shah M, Johns B, Abimiku A, Walker DG. Cost-effectiveness of new WHO recommendations for prevention of mother-to-child transmission of HIV in a resource-limited setting. *AIDS.* May 15 2011;25(8):1093-1102.

31. Claxton K, Martin, S., Soares, M., Rice, N., Spackman, E., Hinde, S., Devlin, N., Smith, P.C., Sculpher, M. *Methods for the estimation of the NICE cost-effectiveness threshold.* Centre for Health Economics, University of York;2013.

32. World Bank. Health expenditure, public (% of GDP). 2013; http://data.worldbank.org/indicator/SH.XPD.PUBL.ZS. Accessed 25/2/2014, 2014.

33. Moreno-Serra R, Smith, P.C. Broader health coverage is good for the nation's health: evidence from country level panel data. *Journal of the Royal Statistical Society.* 2014.